Antibiotic Stewardship in the Neonatal Intensive Care Unit

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Objectives

• 1. Describe antibiotic use in the NICU
• 2. Explain the role of antibiotic stewardship in the NICU
• 3. Provide examples of successful antibiotic stewardship in the NICU

Background

• Antibiotics are the most commonly prescribed medications given to hospitalized children
  – 71% of PICU patients and 43% of NICU patients in a multicenter study (Groshkopf et al, PIDJ 2005)
History of antibiotic use in neonates

• 1950s: Group B Streptococcus was identified as the cause of sepsis in neonates
• 1960s-70s: Antibiotic prophylaxis against GBS and other infections is routinely given to all preterm infants
• 1980s-90s: Strategies to treat mother to prevent GBS transmission are implemented
• 2000s-present: Negative effects of prophylactic antibiotics are increasingly realized

Why should we limit antibiotic use in the NICU?

• Broad spectrum antimicrobial use in the NICU has been linked to
  – Emergence of multi-drug resistant gram negative bacilli
  – Development of invasive candidiasis and colonization with candida
• Prolonged duration of empiric antibiotics for early onset sepsis in ELBW infants has been associated with:
  – Increased mortality
  – Increased rates of NEC

Patel SJ, Saiman L. Principles and strategies of antimicrobial stewardship in the NICU. Semin Perinatol 2012.
Antibiotic resistance

• On March 27, 2015 Obama released a plan to decrease the emergence of antibiotic-resistant bacteria
• This included a plan to:
  – Reduce inappropriate antibiotic use by 50% in outpatient settings and 20% in inpatient settings by the year 2020
  – Establish antibiotic stewardship programs in all acute care hospitals in the U.S.

The Neonatal microbiome

Antibiotic Use and Resistance

• Multi-center study that examined fecal samples from hospitalized NICU infants at time of discharge
• History of prolonged antibiotic use (≥5 days) was associated with increased risk of colonization with resistant gram negative bacilli
  – Resistance seen to gentamicin, 3rd/4th generation cephalosporins, and carbapenems

Necrotizing enterocolitis

• A disease of the gastrointestinal tract that occurs primarily in premature neonates
  – 1-5% of VLBW (<1500g) will develop NEC
  – Mortality associated with NEC is 25-33%
  – Risk factors: prematurity, low birth weight, and alterations in bacterial colonization of the GI tract

Antibiotic Use and NEC in neonates

• Neonates who received antibiotics for “culture-negative” sepsis were found to have significantly increased risk of NEC

How does antibiotic use increase rates of NEC?

• Theory: Changes in the gut microbiome
  • 1 study compared fecal samples from healthy preterm infants (<32 weeks) who received ≤5 days or >5 days of antibiotics
    – Decreased microbial diversity in the infants who received antibiotics for >5 days

Antimicrobial use variation in California NICUs

• California Children’s Services (CCS) has required NICUs to submit antibiotic use data since 2013
• 132/136 NICUs in California participate in the California Perinatal Quality Care Collaborative (CPQCC) which prepares the data
• 127 NICUs were included in this study (52,061 infants and 746,051 patient-days)


Antibiotic use variation in California NICUs

• This study found that “antibiotic-use rates” (the % of days during which a neonate received an antimicrobial agent) varied between NICUs from 2.4% to 97%!!!
• Antibiotic-use rates DID NOT correlate with rates of proven infection, NEC, surgical case volume, or NICU mortality
• The widest variation was seen among “intermediate-level NICUs” which care for the least sick infants
  – Rates were similar to regional NICUs

What are antibiotics being prescribed for?

- Study from UT Southwestern NICU where prospective recording of antibiotic use was performed for 14 months
- 1607 infants received antibiotics for 9165 days (5.7 DOT/infant)
- 94% of antibiotics were empiric for “suspected infection”
- 26% of antibiotics were continued for >5 days despite negative cultures
  - Reasons given were “pneumonia” and “culture-negative sepsis”

Cantey JB et al, PIDJ 2015;34:267-272

CDC 12-Step Campaign to Prevent Antimicrobial Resistance

- Published in 2002
- 4 major strategies:
  - Preventing infection
  - Diagnosing and treating infection effectively
  - Using antimicrobials wisely
  - Preventing transmission of resistant organisms

<table>
<thead>
<tr>
<th>CDC 12 Step Program to Prevent Antimicrobial Resistance: Hospitalized Patients</th>
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<tbody>
<tr>
<td>1. Vaccines</td>
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<tr>
<td>2. Get the catheters out</td>
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<td>3. Target the pathogen</td>
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<td>4. Access the experts</td>
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<td>5. Practice antimicrobial control</td>
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<td>6. Use local data</td>
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<td>7. Treat infection, not contamination</td>
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<td>8. Treat infection, not colonisation</td>
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<td>9. Know when to say “no” to vancomycin</td>
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<td>10. Stop treatment when cured</td>
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<tr>
<td>11. Isolate the pathogen</td>
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<td>12. Break the chain of contagion</td>
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Centers for Disease Control and Prevention (CDC): www.cdc.gov/drugresistance/hospital.html
The CDC’s 12-step program applied to the NICU

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<th>CDC Step</th>
<th>Examples</th>
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<td>4. Target the pathogen</td>
<td>Narrowing treatment when possible, using the appropriate agent</td>
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<tr>
<td>6. Practice antimicrobial control</td>
<td>Limiting post-operative or chest tube prophylaxis</td>
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<td>8. Treat infection, not colonization</td>
<td>Not treating a + blood culture that is a likely contaminant, obtain 2 blood cultures for late-onset sepsis</td>
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<td>9. Know when to say “no” to antibiotics</td>
<td>Not using a very broad spectrum agent empirically, not using redundant coverage</td>
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<tr>
<td>10. Stop treatment when infection is cured</td>
<td>Stopping treatment at an appropriate time</td>
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Patel SJ et al. Antibiotic use in NICUs and adherence with the CDC 12 Step Campaign to prevent antimicrobial resistance. PMJ 2009.

What is antimicrobial stewardship

- Guidance regarding multiple facets of antimicrobial therapy
  - Need for antimicrobials
  - Selection of agents
  - Dosing of agents
  - Route of administration
  - Duration of therapy
- Goal: optimization of clinical outcomes and minimization of unintended consequences of antimicrobial use
  - Includes toxicity, emergence of pathogens such as C. diff, and emergence of resistance

Dellit et al. IDSA and SHEA guidelines for developing an institutional program to enhance antimicrobial stewardship. Clinical infectious diseases 2007.

Does antimicrobial stewardship work?

- Large body of evidence in adults that antimicrobial stewardship:
  - Reduces use of antibiotics and health care costs
  - Can lead to decreased antimicrobial resistance
  - Decreased rates of C. diff infection

CDC Get Smart campaign: http://www.cdc.gov/getsmart/healthcare/evidence.html
Why is antimicrobial stewardship in the NICU challenging?

• Significant consequences of missing an infection
• Nonspecific signs of infection in neonates
• Difficulty in establishing diagnosis of infection
  – Can’t culture PICC lines, only small amounts of blood submitted for culture, invasive procedures often avoided
  – Coagulase negative staph can be a contaminant or pathogen

Who should be involved?

• Typically consists of an infectious disease physician and an infectious disease pharmacist
• Requires support and buy-in from hospital administration, physician leadership, and all providers involved in the care of the neonate

How is stewardship implemented

• (1) Persuasive approach
  – Prescriber audit with intervention and feedback
• (2) Restrictive
  – Formulary restriction and preauthorization
Prescriber audit with intervention and feedback

• The antimicrobial stewardship team reviews antibiotic prescribing and gives feedback to prescribers at initiation and continuation of therapy (48-72 hours)
• Pros: Real-time review and feedback provided
• Cons: Time-intensive

Restrictive approach

• Restricted antimicrobials can be removed from the formulary or require pre-approval
• Pros: The most effective method of controlling antimicrobial use
  – Can be useful as part of a multifaceted response to a nosocomial outbreak of infection
• Cons: May result in shifts to alternative agent, (which subsequently develops resistance), further prescribing advice is not pursued

Other components of stewardship

• Education: necessary to enhance understanding and acceptance of stewardship strategies, but only marginally effective in changing antimicrobial prescribing practices
• Guidelines and clinical pathways: Should incorporate local microbiology and resistance patterns
  – Accessibility may affect implementation
Other components of stewardship

- **Antimicrobial order sets**: may include automatic stop orders (ex. Postoperative prophylaxis)
- **Rapid tests**: Rapid viral testing may be used to discontinue antibiotics early
- **Biomarker-guided clinical decisions**: CRP or other biomarkers can be used to decide duration of therapy

Antibiogram

Pooled data of all microbiologic isolates and susceptibilities during a defined time period

- May be stratified by inpatient versus outpatient, urine versus blood isolates, adult versus pediatric, etc.

What you can do to help with antibiotic use in the NICU

- 1. Ask questions about why, how long, and which antibiotics are being prescribed
- 2. Don’t hesitate to call the peds ID physician on call to review a case
- 3. Monitor for side effects from antibiotics (rash, diarrhea, etc.)
- 4. Educate parents as to why antibiotics are restricted and risks of antibiotics in the neonatal period
Specific examples of NICU stewardship

Antimicrobial stewardship in the NICU

• Retrospective evaluation of implementation of a "multi-disciplinary ID-team" in the tertiary care NICU (The Netherlands) from 1990-2008
• A multi-disciplinary ID-team, consisting of Peds ID, a neonatologist, and microbiologist were contacted daily to discuss antibiotic use, and weekly meetings were held with all providers to discuss all cases of proven or possible infection
• Outcome: Mean days of therapy (DOT) decreased significantly from 9.0 to 5.8 from 1990 to 2008 although there was no change in the number of infants who were treated with antibiotics


Automatic stop dates in EMR

• Prospective study of neonates admitted to a level 3 NICU
• Antibiotics were limited to 48 hours for empiric therapy, and 5 days for pneumonia and culture-negative sepsis by setting automatic stop dates in EMR
• Antibiotic use dropped by 27%, without any increase in recurrence of sepsis or mortality

Potential NICU interventions

- Use of CRP to discontinue antibiotics earlier than a fixed treatment course
  - CRP usually increases at 12-24 hours after infection and peaks at 24-48 hours
  - Initially has poor sensitivity, but serial values increase sensitivity up to 97.5% (high negative predictive value)
- Use of procalcitonin to discontinue antibiotics early in neonates with possible early-onset sepsis
  - PCT concentrations rise within 6-8 hours after endotoxin exposure and plateau at 12 hours

CRP to shorten therapy for late-onset sepsis (LOS)

- Prospective study of infants <4 weeks old who were diagnosed with culture positive LOS
- Implemented a pathway in which CRP was measured every 48 hours, and antibiotics were discontinued when <12 mg/L (n=138); this was compared to historical controls (n=85)
- Outcome: Infants in intervention group were treated for 9 versus 16 days (p<0.001), with no increase in mortality or relapsed infection rates

Procalcitonin (PCT) in early onset sepsis

- Prospective, randomized study of neonates >34 weeks GA at single tertiary NICU/PICU over 18-month study period
- Neonates with suspected sepsis in first 3 days of life were randomly assigned to treatment based on conventional lab parameters (I:T ratio, CRP) or PCT-guided therapy
  - Conventional: Abx for minimum of 48 hours
  - PCT: Abx d/c'ed if 2 consecutive PCT values below age cutoff values
- Outcome: PCT-guided decision-making resulted in 22.4 hour decrease in antibiotic therapy